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(21) International Application Number: PCT/GB89/00427 (22) International Filing Date: 21 April 1989 (21.04.89) (30) Priority data: 8809616.9 22 April 1988 (22.04.88) GB (71) Applicant (for all designated States except US): CANCER RESEARCH CAMPAIGN TECHNOLOGY LIMITED [GB/GB]; 2 Carlton House Terrace, London SW1Y 5AR (GB). (72) Inventors; and (75) Inventors/Applicants (for US only) : BAGSHAW, Kenneth, D. [GB/GB]; ROGERS, Gordon, T. [GB/GB]; CRC Laboratories, Department of Medical Oncology, Charing Cross Hospital, Fulham Palace Road, London W6 8RF (GB). SHARMA, Surinder, K. [GB/GB]; CRC Laboratoires, Department of Medical Oncology, Charing Cross Hospital, Fulham Palace Road, London W6 8RF (GB).		(74) Agents: GOLDIN, Douglas, Michael et al.; J.A. Kemp & Co., 14 South Square, Gray's Inn, London WC1R 5EU (GB). (81) Designated States: AT (European patent), BE (European patent), CH (European patent), DE (European patent), FR (European patent), GB (European patent), IT (European patent), JP, LU (European patent), NL (European patent), SE (European patent), US. Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: FURTHER IMPROVEMENTS RELATING TO DRUG DELIVERY SYSTEMS (57) Abstract A three component system, for use in association with one another, in the treatment of malignant diseases comprises: a first component which is a substance or conjugation of substances characterised by (a) one or more molecular configurations that are complementary to molecular configurations associated with malignant cells, such that the first component tends to localise selectively at sites of malignant cells and (b) additionally by one or more catalytic sites; a second component which is able to bind to such part of the first component so as to inactivate the catalytic site of the first component and/or accelerates the clearance of the first component from the blood when the first and second components are administered clinically and a third component which is a substrate for the catalytic site on the first component, one of the end products of the catalysis being a substance which is more cytotoxic to malignant cells than the third component. The use of the second component reduces the extent to which the cytotoxic drug is released from the third component in regions of a patients body remote from the target tumour.		

TITLE: FURTHER IMPROVEMENTS RELATING TO DRUG
DELIVERY SYSTEMS

THIS INVENTION relates to methods and systems for the control of neoplastic cell growth and is particularly concerned with methods and systems involving the localisation of cytotoxic agents at tumour sites.

5 In our earlier Patent Application PCT/GB88/00181 we disclose a two-component system which comprises

(i) a first component (Component A-E) that is an antibody fragment capable of binding with a tumour
10 associated antigen, the antibody fragment being bound to an enzyme capable of converting a prodrug into a cytotoxic drug;

(ii) a second or final component (Component PD) that is a prodrug convertible under the influence of the enzyme
15 to a cytotoxic drug (CD).

In our earlier PCT Patent Application and in this present Patent Application, the word 'tumour' is to be understood as referring to all forms of neoplastic cell growth including carcinomas, sarcomas, lymphomas and leukaemias.

20 Our existing system is used to target cytotoxic prodrugs to the site of neoplastic cell growth. However, although this two-component system is useful in the control of tumours, the amount of first component that localises per gram of tumour in humans may be less than

component which is a substance or conjugation of substances characterised by (a) one or more molecular configurations that are complementary to molecular configurations associated with malignant cells, such that the first component tends to localise selectively at sites of malignant cells and (b) additionally by one or more catalytic sites; a second component which is able to bind to such part of the first component so as to inactivate the catalytic site of the first component and/or accelerates the clearance of the first component from the blood when the first and second components are administered clinically; a third component which is a substrate for the catalytic site on the first component, one of the end products of the catalysis being a substance which is more cytotoxic to malignant cells than the third component.

The clinically most useful form of the first component is a conjugate of an antibody or fragment thereof and an enzyme while the clinically most useful form of the third component is a prodrug convertible under the influence of the enzyme activity of the first component into a cytotoxic compound. The antibody will desirably be one recognising and binding preferentially to a tumour associated antigen and it will be apparent to those skilled in the art how to match the antigen

affinity to other tumour-associated compounds.

In one embodiment of the system of the invention the first component is a conjugate of an antibody to a tumour-associated antigen or a fragment thereof that
5 includes the antigen binding site of the antibody, said antibody or fragment thereof being conjugated directly, or indirectly through a linking component, to an enzyme or to an antibody or antibody fragment with catalytic functions. In this case the conjugation can be effected by chemical
10 bonding or by splicing together nucleic acid sequences that code at least for one or more antigen binding sites and one or more catalytic sites and such other sequences as are necessary to retain the vector function of the molecule and the catalytic function of the peptide when
15 the gene product of the reconstructed nucleic acid sequence is expressed by eukaryotic or prokaryotic cells.

In a further embodiment, the antibody in the first component is bivalent and formed by bonding together two univalent antibody fragments, or by recombinant DNA
20 techniques, one fragment having affinity for a tumour marker substance, the other having affinity for an enzyme. In such a case the conjugate can be formed either in vitro prior to administration or in vivo by first administering the bivalent antibody, allowing time for it to localise at
25 tumour sites and then administering the enzyme for

including enzymes, are immunogenic in mammalian species including man.

The present system will be most effective in man and suitable for repetitive use when the immunogenicity of a first component antibody-enzyme conjugate is minimised or if immune tolerance to such conjugates has been induced. This is likely to be achieved through genetic engineering methods since the production of monoclonals to specific antigens by human hybridomas has so far proved difficult to achieve consistently. It has been shown that the antigen binding site of a rodent monoclonal antibody can be incorporated into a human immunoglobulin framework (Reichmann et al, Nature 332: 323-327, 1988).

It has also been shown that antibodies can be produced which function as enzymes (Pollack SJ et al, Science 234, 1570-1573, 1986) so the ultimate form of the antibody-enzyme conjugate may be a human immunoglobulin construct expressing one or more antigen binding sites characterised by peptide sequences of non-human origin and one or more catalytic sites.

With a 'humanised' antibody conjugated to a human enzyme or a non-human enzyme which has been rendered non-immunogenic in man, or a construct with both antigen binding and catalytic sites on a human immunoglobulin, the second component of our system will need to be directed at

galactose residues or residues of other sugars such as lactose or mannose, so that it can bind enzyme in plasma but be removed together with the enzyme or antibody-enzyme conjugate from plasma by receptors for galactose or other
5 sugars in the liver in a period of time such that the antibody does not, to any appreciable extent, enter the extravascular space of the tumour where it could inactivate tumour localised enzyme. In this case,
10 galactose residues in the second component are either chemically added or exposed by removing terminal sialic acid residues.

Terminal sialic residues play a role in maintaining the presence of glycoproteins in the blood.
15 Removal of terminal sialic acid by neuraminidase exposes proximal sugar residues such as galactose. Desialylated proteins are rapidly removed from the blood by receptors in liver and possibly other sites. (Morell et al, J.Biol. Chem. 246: 1461-1467, 1971).

20 Asialo human chorionic gonadotrophin was prepared by digesting 1 mg of a glycoprotein in 1 ml of 0.05M sodium acetate buffer, pH 5.6, containing 0.15M NaCl with 20ug of neuraminidase (Sigma Type II from Vibrio cholerae) at 37° for 30 minutes. The neuraminidase was
25 then removed. Sialo and Asialo preparations were compared for clearance in A2G mice. T 1/2 for the sialyted hCG was

substances could be identified or developed for the same purpose.

A further embodiment of the invention is one wherein the second component is conjugated to a
5 macromolecule such as a dextran, liposome, albumin microsphere or macroglobulin with a molecular weight in excess of 500,000 Daltons or a biodegradable particle such as a blood group O erythrocyte so that the second component is restrained from leaving the vascular
10 compartment by virtue of the size of the conjugate.

A further embodiment of the invention is one wherein the second component is an antigen, hapten or protein construct bearing an epitope capable of binding with the first component to form complexes having
15 accelerated clearance from plasma.

In a still further modification of the system, the first component is covalently linked to biotin or derivatives of biotin, and the second component then comprises the biotin-binding glycoprotein avidin found in
20 egg white, or streptavidin, itself optionally covalently linked to galactose.

Biotin may be conjugated to antibody or fragment thereof by reaction with a 10 molar excess of sulphosuccinimidyl 6-(biotinamido)hexanoate at pH 8.5 at
25 4°C for 16 hours. The product is purified by

tumour sites in a comparable fashion to antibody. There are literature examples of radiolabelled hormones, growth factors and metabolites localising in tumours (Krenning et al, Lancet i 242-244, 1989 (Somatostatin); Hattner et al, Am. J. Roentgenol. 143: 373-374, 1984) but in none of these were the vectors used to convey enzyme to tumour sites.

The enzyme part of the first component can be of human or non-human origin. The advantage of using an enzyme of human origin lies in avoiding or minimising the immunogenic effect of an enzyme of non-human origin. The disadvantage of an enzyme of human origin is the probability that the presence of enzyme in human tissues will activate the prodrug, thus releasing active drug at the non-tumour sites. However, it may be possible to identify certain human enzymes which are so distributed that this activation would not cause a serious problem. Also, inactivation of such enzymes in tissues might be achieved by using high affinity anti-enzyme antibody fragments which would be rapidly cleared from the plasma before giving the first component conjugate. Where the human enzyme is normally present in the plasma, this would activate prodrug in the plasma which would be highly disadvantageous and be liable to cause general toxic effects. Administration of an appropriately selected

Abuchowsky A., van Es T., Palezuk NC, Davis FF - J. Biol. Chem. 252: (11), 3578-81, 1977, or
Kawamura K, Igarishji, T, Fujii T., Kamasaki J., Wada, H., Kishimoto, S. Int. Arch. Allergy appl. Immunol. 76:
5 324-330, 1985.

To minimise clinical problems arising from the use of immunogenic antibody enzyme conjugates and immunogenic antibodies or avidin-like constructs, it is desirable to minimise or delay the production of host
10 antibodies to xenospecific proteins by using immunosuppressive agents such as cyclosporin, cyclophosphamide, methotrexate, azathioprine etc., in order to provide sufficient time for the delivery of repeated treatments.

15 The ability of cyclosporin to prevent antimurine antibody responses by rabbits and in patients has been demonstrated. See, for example, Ledermann, JA. Begent, RHJ. Bagshawe, KD. Br. J. Cancer, 58: 562-566, 1988, or Ledermann, JA. Begent, RHJ. Riggs, SJ. Searle, F. Glaser,
20 MG, Green, AJ. Dale, RG. Br. J. Cancer 58: 654-657, 1988.

In certain clinical conditions, it can be advantageous for the first component to be conjugated to a signal producing molecule such as a radioisotope suitable for scintigraphic imaging by gamma camera so as to confirm

than one vector to carry enzyme to tumour sites. Multiple vectors may permit greater or more economical delivery of enzyme to tumour sites. It may also be advantageous to use more than one type of prodrug to generate a state
5 equivalent to multidrug chemotherapy so as to reduce the risks of drug resistance and this in turn may require the use in treatment of more than one type of enzyme. These variations may in time require the use of more than one second component to achieve the required clearing of
10 enzymes from plasma and other non-tumour sites.

The three components forming the system of the present invention are designed to be used in association with one another in a method of treatment of the human or animal body by therapy.

15 It is specifically designed for use in a method for the treatment of malignant diseases including carcinomas, sarcomas, lymphomas and leukaemias which comprises administering to a host in need of such treatment an effective amount of a system.

20 In such a method, the first component is administered first, the second component is administered subsequent to the first component after a time interval such that the first component has selectively localised at the site of malignant cells and the third component is
25 administered subsequent to the second component after a

falling to 40 units/ml activity after 24 hours). In the wells containing the antibody (hybridoma supernatant) the activity was reduced to 13.0 carboxypeptidase units/ml. The antibody alone had no effect on the optical density of methotrexate. These experiments show that the enzyme active site on the carboxypeptidase can be substantially inactivated by an antibody raised against the enzyme. Monoclonal antibodies to carboxypeptidase G₂, raised by the technique described above will only have a similar enzyme inhibiting property if they are directed at epitopes in or close to the active site of the enzyme.

EXAMPLE 2

Evidence for localisation of antibody-enzyme conjugate at tumour sites

1. 4 nude mice bearing LS174T human colon cancer xenografts on their L flanks were injected with A5B7 (Fab')₂ monoclonal antibody directed at carcinoembryonic antigen conjugated to carboxypeptidase G2 and labelled with ¹²⁵I. An immunoscintigraph taken after 48 hours confirms localisation of the conjugate at the tumour sites.

Similar results were obtained using the following conjugates:

IgG or F(ab')₂ in 0.2M sodium phosphate buffer, pH 8.6, at a concentration of 4 mg/ml was treated with a 15 molar excess of SPDP in ethanol and left at r.t. for 1 hour. Excess SPDP was removed on a column of Sephadex G-25 equilibrated in 0.1M sodium acetate buffer, pH 4.5. The pyridyldisulphide group was then reduced for 30 minutes with 50 ul/ml of 100 mM dithiothreitol and excess reducing agent removed by Sephadex G-25 gel filtration.

3) Derivatisation of carboxypeptidase.

Carboxypeptidase in 0.1M sodium phosphate buffer, pH 7.6 (containing 372 mg EDTA/litre) at 2 mg/2.5 ml was treated for 3 hours with a 15 molar excess of succinimidyl 4-(p-maleimidophenyl)butyrate (SMPB) dissolved in THF. The excess SMPB was removed by gel filtration on Sephadex G-25.

4) Conjugation

The derivatised enzyme was mixed with an equimolar amount of thiolated antibody and the progress of the conjugation monitored by gel filtration. When no further reaction was judged to take place the mixture was concentrated and the conjugate purified by gel filtration.

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SAMPLE	TIME	COUNTS (1)	CPM (1)	%CV	
1	30	1092	2171.4	3.1	(Negative Control- SB10-Anti-hCG)
2	30	805	1588.6	3.6	"
3	30	16428	33278.0	.8	SB43 x 20
5 4	30	23339	47302.9	.7	"
5	30	22020	44679.3	.7	SB43 x 100
6	30	22096	44833.8	.7	"
7	30	8437	16873.4	1.1	SB43 x 1000
8	30	7671	15336.8	1.1	"
10 9	30	15411	31052.2	.8	SB43-Gal-10x20
10	30	15418	31066.3	.8	"

EXAMPLE 4Evidence that SB43 inactivates/clears Ab-E-conjugate in vivo from plasma

The level of carboxypeptidase G2 activity in plasma can be monitored by observing the hydrolytic cleavage of methotrexate, a folic acid analogue, to pterates and L-glutamate. When a conjugate of A5B7-F(ab')₂-carboxypeptidase G2 (25 enzyme units) was injected intravenously and plasma samples obtained 20 hours later significant hydrolysis of methotrexate was observed equivalent to 1.12 to 1.45 enzyme units/ml as shown by the steps of the spectrophotometric print-out.

Affinity purified avidin was used as obtained from Sigma Ltd., 10-15 units/mg protein. Mice received 20 ug of biotinylated A5B7-carboxypeptidase G2 conjugate followed after one hour by avidin in the dose range 5 20-500 ug. Rapid clearance of the enzyme activity in plasma was observed comparable to that observed with SB43 monoclonal antibody in Example 4.

EXAMPLE 6

IgG class immunoglobulins carrying different 10 specificities on their two binding sites can be made by a fusion technique employing hybridomas producing different antibodies (Milstein C & Cuello AC. Nature 305: 537-540, 1983; Sfaerz UD & Bevan MJ. Proc. Nat. Acad. Sci. USA 83: 1453-1457, 1986) or by chemical conjugation of univalent 15 preparations of each of the antibodies required as used here. $F(ab')_2$ fragments of monoclonals SB10 (anti-human chorionic gonadotrophin (anti-hCG)) and A5B7 (anti-carcinoembryonic antigen, (anti-CEA)) were reduced in the presence of arsenite. $F(ab')_2$ fragment (20 mg) in 20 0.1M sodium phosphate buffer pH 7.6 (10 ml) was mixed with sodium arsenite (12.4 mg) EDTA (3.72 mg) and 2-mercapto-ethylamine (1.13 mg) and left at room temperature. Solid 5,5'-dithio-bis-(2-nitrobenzoic acid)

	anti CEA/ anti hCG	non-specific F(ab') ₂
	blood 2.9	0.6
	liver 3.9	1.9
	kidney 1.8	1.2
5	lung 3.2	1.2
	spleen 6	3.0
	colon 9	5.3

(Conjugation of A5B7 and SB43 (anticarboxypeptidase) has not yet been performed but above experiment demonstrates retention of binding site function).

EXAMPLE 7

Method for galactosylation

Cyanomethyl 2,3,4,6-tetra-O-acetyl-1-thio-β-D) galactopyranoside (400 mg) in anhydrous methanol (10 ml) was treated with 5.4 mg of sodium methoxide in 1 ml of anhydrous methanol at about 20°C for 48 hours. A stock solution of IgG in 0.25M sodium borate buffer, pH 8.5 at 1.3 mg/ml was prepared. Since the number of galactose residues conjugated to IgG was not determined, a unitage was adopted corresponding to the number of microlitres of the activated galactose derivative added to 200 ug of IgG at a concentration of 1.3 mg/ml.

Figure 1B shows the levels of active drug in various tissues in mice which had not received SB43-Gal 10 clearing antibody with those that had. In the absence of SB43-Gal 10 clearing antibody, levels of active drug were significantly lower than those found in liver and lung but in animals receiving the SB43-Gal 10 clearing antibody tumour levels were higher than in any other tissue.

As part of the same experiment two groups of mice, one with and one without SB43-Gal 10, were killed without receiving the prodrug. The tissues were extracted and tested for ability to convert prodrug to active drug in vitro. The results are shown in the Table and expressed as percentage of injected dose of carboxypeptidase per gram of tissue.

15 <u>In vivo admin</u>	<u>Carboxypeptidase G2% i.v. dose per gram of tissue at 48 hours</u>		
	Tumour	Plasma	T/P
Ab-CPG2	8.1(+0.69)	0.22	36
AB-CPG2	7.2(+1.42)	0.026	277
+			
Gal 10 antiCPG2			
24 hours later			

F(ab')₂-CP 50 units resulted in death of the animals and this was shown to be due to persisting enzyme activity in the blood.

Figure 2b shows accelerated clearance of 20 ug
5 monoclonal ¹²⁵I-SB43 anticarboxypeptidase from the blood of A2G mice when 77 ug of the corresponding antigen, carboxypeptidase G2, was administered 1 hour later compared with controls which did not receive the antigen.

These data indicate that accelerated clearance
10 of an administered antibody can be achieved by administration of a substance expressing the epitope corresponding to the binding site of the antibody.

EXAMPLE 9

Conjugation of TCK9 human albumin microspheres to SB43

15 1 mg of TCK9 human polyalbumin microspheres were derivatised with a 12.5M excess of sulpho-MBS (based on monomeric unit of 66 Kd) in a total of 1 ml phosphate buffer pH 7.8 for 2 hours at about 20°C. The mixture was centrifuged at 3000 rpm for 3 minutes and resuspended in 1
20 ml of buffer, and rewashed once more. 1.5 mg of ¹²⁵I labelled SB43 was thiolated by 20M excess of SPDP, according to manufacturers (Pharmacia) instructions, at

CLAIMS

1. A three component system, for use in association with one another, in the treatment of malignant diseases comprising: a first component which is a substance or conjugation of substances characterised by (a) one or more
5 molecular configurations that are complementary to molecular configurations associated with malignant cells, such that the first component tends to localise selectively at sites of malignant cells and (b) additionally by one or more catalytic sites; a second
10 component which is able to bind to such part of the first component so as to inactivate the catalytic site of the first component and/or accelerate the clearance of the first component from the blood when the first and second components are administered clinically and a third
15 component which is a substrate for the catalytic site on the first component, one of the end products of the catalysis being a substance which is more cytotoxic to malignant cells than the third component.
2. A system according to claim 1 wherein the first
20 component or a part of the first component is biotinylated and in which the second component is avidin or other protein with a high affinity for binding to biotinylated proteins.
3. A system according to claim 1 wherein the first
25 component is a conjugate of an antibody to a tumour associated antigen or a fragment thereof that includes the antigen binding site of the antibody, said antibody or

human immunoglobulin, or fragment thereof, having antigen binding site(s) of human origin or having antigen binding site(s) of non-human species.

8. A system according to any one of the preceding
5 claims wherein the second component is an antibody or fragment thereof having an affinity for an antigen binding site of an antibody of the first component or the active site of an enzyme of the first component or another constituent part of the first component.
- 10 9. A system according to any one of the preceding claims wherein the second component is one causing rapid loss of enzyme activity of the first component in plasma without incurring significant loss of enzyme activity from tumour sites.
- 15 10. A system according to claim 9 wherein the second component includes a sufficient number of covalently bound galactose residues or residues of other sugars such as lactose or mannose, so that it can bind enzyme in plasma but be removed together with the enzyme or antibody-enzyme
20 conjugate from plasma by receptors for galactose or other sugars in the liver in a period of time such that the antibody does not, to any appreciable extent, enter the extravascular space of the tumour where it could inactivate tumour localised enzyme.
- 25 11. A system according to claim 10 wherein galactose residues in the second component are exposed by removing terminal sialic acid residues.

16. A system according to any one of the preceding claims wherein the first component includes an enzyme of human or non-human origin.
17. A system according to claim 16 wherein the enzyme is of non-human origin but modified by amino acid substitutions to minimise its immunogenicity in man.
18. A system according to claim 17 wherein the enzyme is conjugated to residues such as polyethylene glycol, or other polymers to reduce immunogenicity.
19. A system according to any one of the preceding claims wherein the first component is conjugated to a signal producing molecule such as a radioisotope suitable for scintigraphic imaging by gamma camera so as to confirm localisation of the first component at tumour sites.
20. A system according to any one of the preceding claims including more than one type of first component and/or more than one type of second component and/or more than one type of third component.
21. A system according to any one of the preceding claims for use in association with cyclosporin or other immunosuppressive drug or antibody to inhibit antibody response in the host to the system.
22. A system according to any one of the preceding claims for use in a method of treatment of one human or animal body by therapy.
23. A method for the treatment of malignant disease including carcinomas, sarcomas, lymphomas and leukaemias

Fig. 1A.

1/2

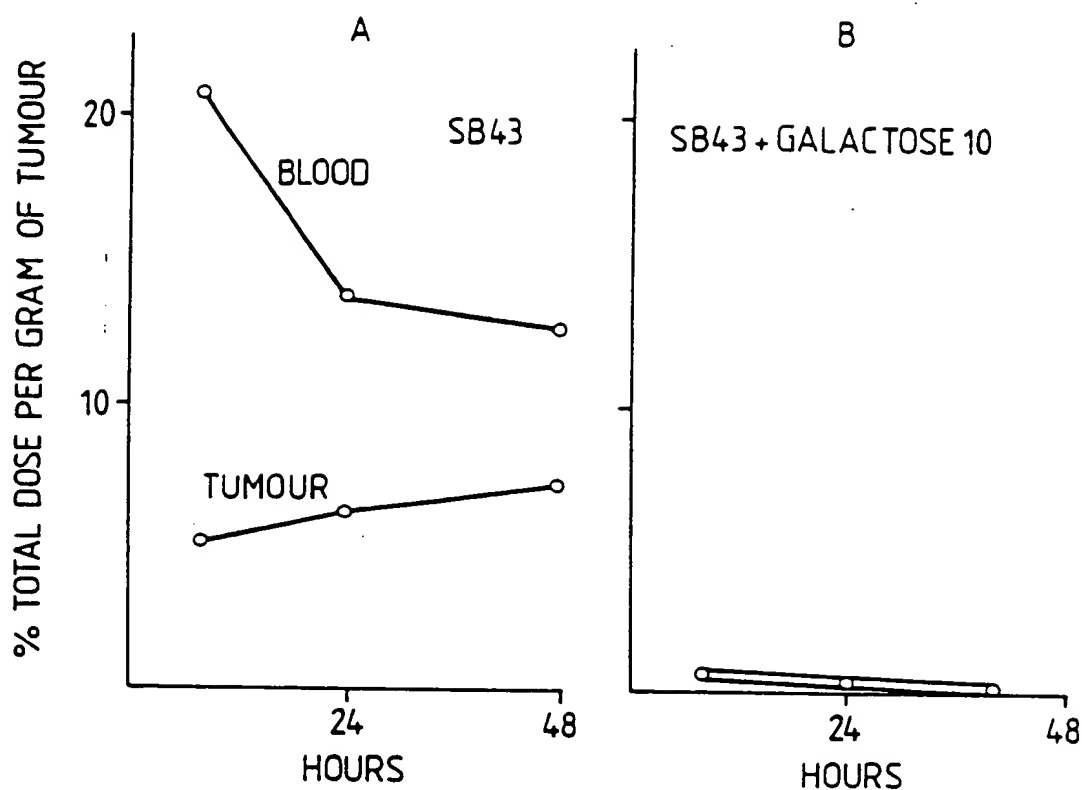
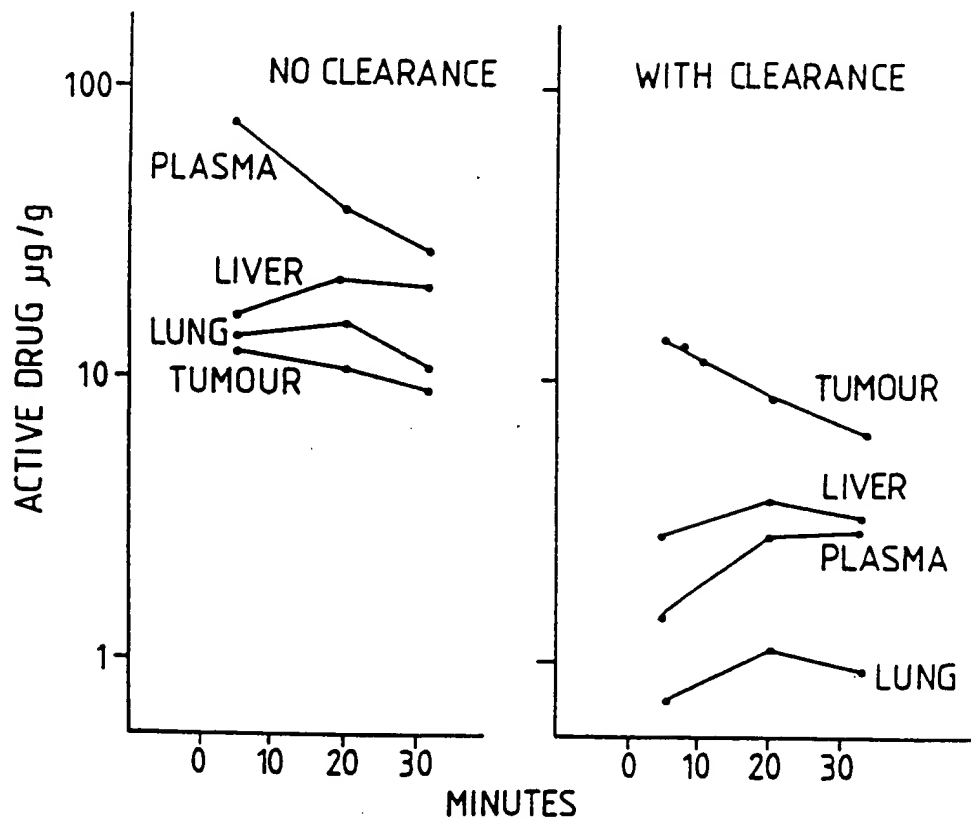


Fig. 1B.



ACTIVE DRUG MEASURED (HPLC) AS CONVERSION OF PRODRUG BY TISSUE EXTRACT AT INTERVALS FOLLOWING SB43 GAL 10 CLEARING A/B.

Fig. 2A.

2/2

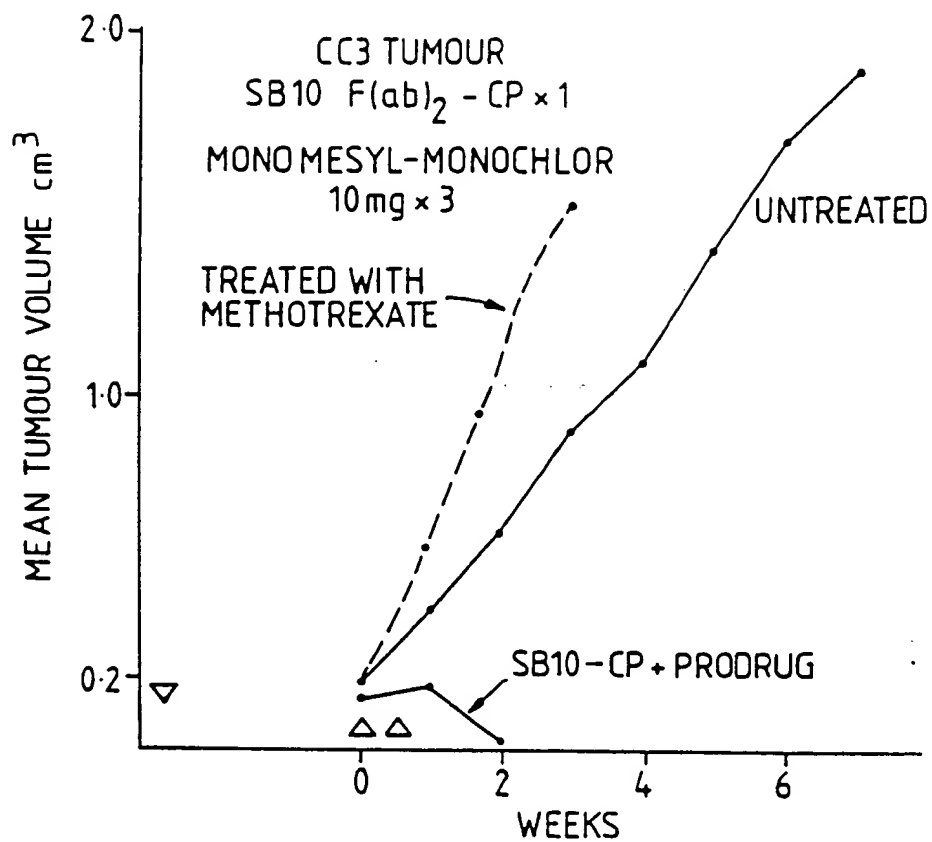
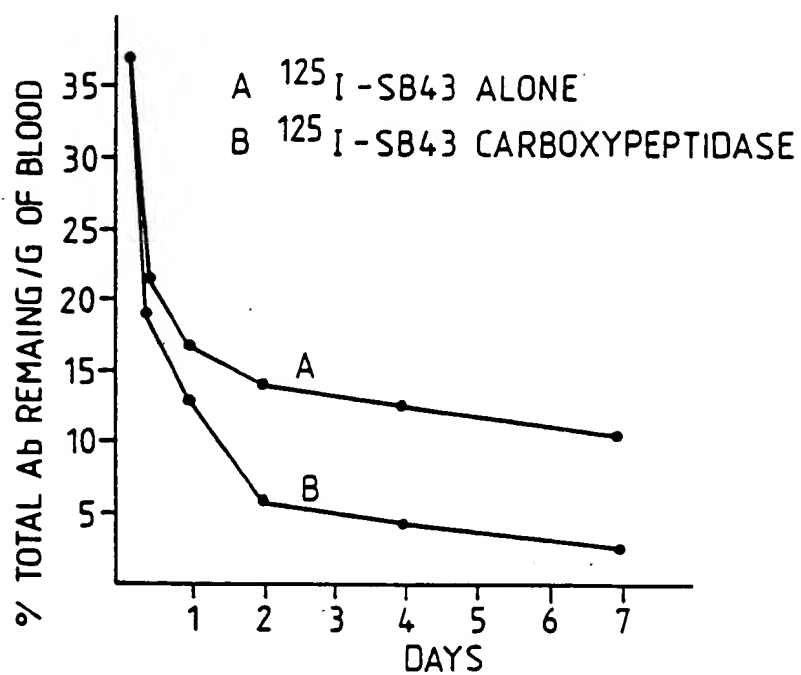


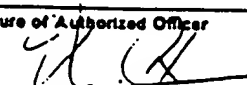
Fig. 2B.



SUBSTITUTE SHEET

INTERNATIONAL SEARCH REPORT

International Application No PCT/GB 89/00427

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all) ⁴ According to International Patent Classification (IPC) or to both National Classification and IPC IPC ⁴ : A 61 K 39/395, A 61 K 39/44, A 61 K 45/05		
II. FIELDS SEARCHED		
Minimum Documentation Searched ⁷		
Classification System	Classification Symbols	
IPC ⁴	A 61 K	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁸		
III. DOCUMENTS CONSIDERED TO BE RELEVANT ⁹		
Category ⁹	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
A	EP, A, 0140728 (SANOFI) 8 May 1985 --	1-22
A	EP, A, 0186551 (SANOFI) 2 July 1986 --	1-22
A	EP, A, 0089880 (SANOFI) 28 September 1983 --	1-22
A,P	WO, A, 88/07378 (CANCER RESEARCH CAMPAIGN TECHNOLOGY LTD) 6 October 1988 -----	1-22
<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p>¹⁰ Special categories of cited documents:</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 45%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"A" document member of the same patent family</p> </div> </div>		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search		Date of Mailing of this International Search Report
18th August 1989		22. 09. 89
International Searching Authority		Signature of Authorized Officer
EUROPEAN PATENT OFFICE		 L. ROSSI

ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO.

GB 8900427
SA 28296

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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		JP-A- 61027926	07-02-86
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		US-A- 4762707	09-08-88
WO-A- 8807378	06-10-88	None	

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